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Original Contribution

Parental Occupational Exposure to Pesticides and Childhood Germ-Cell Tumors

Zhi Chen[1], Patricia A. Stewart[2], Stella Davies[3], Roger Giller[4], Mark Krailo[5], Mary Davis[6], Leslie Robison[7], and Xiao-Ou Shu[1]

[1] Department of Medicine, Vanderbilt-Ingram Cancer Center, and Center for Health Services Research, Vanderbilt University, Nashville, TN.
[2] Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.
[3] Cincinnati Children's Hospital and Medical Center, Cincinnati, OH.
[4] The Children's Hospital, Denver, CO.
[5] Keck School of Medicine, University of Southern California, Los Angeles, CA.
[6] Division of Pediatric Pathology, Riley Hospital for Children, Indianapolis, IN.
[7] Division of Epidemiology and Clinical Research, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN.

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In a recently completed US case-control study (Children's Oncology Group, 1993–2001) with 253 cases and 394 controls, the authors investigated the association between parental occupational exposure to pesticides and risk of childhood germ-cell tumors. Information on occupational pesticide exposure was collected using job-specific module questionnaires and assessed by an experienced industrial hygienist. Odds ratios for childhood germ-cell tumors associated with maternal exposures before pregnancy, during pregnancy, and after the birth of the index child were 1.0 (95% confidence interval (CI): 0.8, 1.4), 1.1 (95% CI: 0.7, 1.6), and 1.3 (95% CI: 0.9, 1.8), respectively. Paternal exposures before pregnancy, during pregnancy, and after the birth of the index child were not related to germ-cell tumors (odds ratios (ORs) were 0.9 (95% CI: 0.7, 1.2), 0.8 (95% CI: 0.5, 1.2), and 0.8 (95% CI: 0.5, 1.3), respectively). When both parents had ever been occupationally exposed to pesticides before the index pregnancy, the odds ratio was 0.8 (95% CI: 0.4, 1.3). Subgroup analyses showed a positive association between maternal exposure to herbicides during the postnatal period and risk of germ-cell tumors in girls (OR = 2.3, 95% CI: 1.0, 5.2) and an inverse association between paternal exposure to pesticides during the index pregnancy and germ-cell tumors in boys (OR = 0.2, 95% CI: 0.1, 1.0). This study did not provide strong evidence supporting a relation between parental pesticide exposure in the workplace and risk of germ-cell tumors among offspring.

case-control studies; child; germinoma; occupational exposure; pesticides

Abbreviations: CI, confidence interval; COG, Children's Oncology Group; SES, socioeconomic status.

The incidence of childhood malignant germ-cell tumors rose during the years 1962–1995 (1–4). In the United States, approximately four children per million under age 15 years were afflicted with germ-cell tumors between 1973 and 1982 (5), and incidence has been increasing (1, 3). Previous studies have suggested that pesticide exposure may lead to germ-cell mutation (6, 7). Over the past few decades, parental exposure to pesticides has received considerable attention as a potential risk factor for childhood germ-cell tumors, but study results have been inconsistent (8–11). In those studies, exposure was estimated simply by whether parents had ever held jobs involving pesticide exposure.

Correspondence to Dr. Xiao-Ou Shu, Center for Health Services Research, Vanderbilt University, 6th Floor Medical Center East, Room 6009, Nashville, TN 37232-8300 (e-mail: Xiao-Ou.Shu@vanderbilt.edu).

However, job titles are generally poor proxies for identifying and quantifying specific exposures (12); therefore, the observed associations with disease are only speculative. Interpretation of previous studies has also been hampered by imprecise risk estimates due to small study populations and low prevalences of exposure.

From 1996 to 2003, the Children's Oncology Group (COG) conducted a large-scale US case-control study of childhood germ-cell tumors. Occupation-specific questionnaires were used to collect information on various exposures, including maternal and paternal exposures to pesticides before conception, during gestation, and during the early childhood of the index child.

MATERIALS AND METHODS

The COG is a cooperative pediatric clinical trials group that treats over 93 percent of childhood cancers in the United States (13). Cases were recruited through COG institutes and included children younger than age 15 years who had been diagnosed with a germ-cell tumor (including germinoma, dysgerminoma, seminoma, embryonal carcinoma, yolk-sac tumor, choriocarcinoma, immature teratoma, and mixed germ-cell tumor) at any anatomic site, except for encephalocele, which is extremely rare and difficult to accurately diagnose. To be eligible for the study, cases must have received a diagnosis of germ-cell carcinoma between January 1, 1993, and December 31, 2001, and be registered with the COG Statistics and Data Center (Arcadia, California). There had to be a telephone in the patient's residence, and the patient's biologic mother had to speak English. Permission to interview was obtained first from the child's physician and then from the parents. COG institutes that had no institutional review board approval for the germ-cell tumor study had no mandatory requirement to register all childhood germ-cell tumor patients; thus, the total number of germ-cell tumor cases treated by all COG institutes was not available.

Of the 496 potentially eligible case children registered with the COG during the study period, 344 met the study eligibility criteria. Seventy case children were excluded because of pathology or age, and 26 were excluded because their tumor was in the brain. Other exclusions were due to physician refusal ($n = 20$), language (mother did not speak English; $n = 32$), or the biologic mother's not being available for interview ($n = 4$). Telephone interviews were completed successfully with the mothers of 278 of the 344 eligible cases (80.8 percent), including the mothers of eight deceased children. Among nonparticipating parents, 44 refused (12.8 percent), 20 had nonworking phone numbers (5.8 percent), and two were unable to schedule an interview.

Controls were selected by random digit dialing and were frequency-matched to cases on the basis of the child's sex, year of birth (± 1 year), and geographic location at diagnosis. The matching ratio was approximately 1:2 for males and 1:1 for females. The different matching ratio used for males and females was designed to maximize study power, because the incidence of germ-cell tumors is much lower among boys than among girls. Before the study was implemented, a frequency matrix for control selection (by birth calendar year and sex) was generated on the basis of the age and sex distribution of germ-cell tumor cases using information obtained from the Children's Cancer Group (now part of the COG) database. Geographic matching was implemented only at the state level. Control phone numbers were generated by keeping the area code and exchange (i.e., the first six digits) of the cases' phone numbers and randomly modifying the last four digits. If a randomly selected phone number was not residential, another phone number was randomly selected by the same method. A randomly selected number was dialed until a family with children under age 15 years was identified or until a predetermined number of phone calls had been made (15 calls, five made during the day on weekdays, five made on weekday evenings, and five made on weekends). A detailed description of this method has been given elsewhere (14, 15).

Of 17,292 randomly selected phone numbers, 5,912 were found to be residential. Of these, 634 were for families who were recruited successfully and had at least one eligible child. The remaining phone numbers were for families who were without eligible children ($n = 3{,}105$), refused to be screened ($n = 325$), or could not be contacted ($n = 1{,}848$). This yielded a screening success rate of 63.2 percent. For families with more than one eligible child, only one child was randomly selected to participate in the study. A telephone interview with the mother was completed successfully for 423 of the 634 potential controls (66.7 percent). Nonresponse was due to refusal ($n = 182$; 28.7 percent), changes in phone numbers ($n = 28$; 4.4 percent), and other reasons ($n = 1$).

Information was obtained from each child's mother through a self-administered questionnaire and a telephone interview. The father was also interviewed when available (223 cases and 285 controls; 80.2 percent and 67.4 percent of the participating cases and controls, respectively). Additionally, 35 case mothers (12.6 percent) and 97 control mothers (22.9 percent) provided a surrogate interview for paternal exposures. The questionnaire included questions about demographic factors, medication use, radiographic exposures, personal habits, lifetime occupational history, and family medical history. The occupational data collected consisted of two parts: a self-administered generic work history (job title, type of business, location of employer, job tasks, number of working hours, primary job activities or duties, and chemicals and equipment used for all jobs that parents had held for 6 months or longer since the age of 18) and interviewer-implemented module questionnaires with detailed job-specific questions (16). Module questionnaires in our study were designed by an industrial hygienist (P. A. S.) for a variety of jobs and exposures (17, 18). A total of 63 job module questionnaires were used in the study. Based on information obtained from the generic work history, up to five module questionnaires were administered to the parents of each participant. If parents had held more than five jobs, priorities were assigned in the following order: 1) the job held during pregnancy, 2) the job held immediately before and after pregnancy, and 3) the job held for the longest time. Questionnaires specifically involved in pesticide assessments comprised those designed for farmers, farmworkers, gardeners, pesticide applicators, carpenters, firefighters, and janitors.

Occupations and industries were coded using the 1980 US Bureau of the Census classification system of jobs and

industries (19). Three broad classes of pesticides (i.e., insecticides, herbicides, and agricultural fungicides) were evaluated using a job exposure matrix approach. This method was developed by our study industrial hygienist (P. A. S.) on the basis of an extensive review of the industrial hygiene literature related to the likelihood of pesticides' being used and their probable quantities, and has been employed in several previous studies (20–22). Using the detailed work history, module questionnaire, and job exposure matrix information, we assigned a score for the probability, frequency, and intensity of pesticide exposure and a confidence score for the exposures of interest to each study participant, with case-control status masked (21). The industrial hygiene literature review estimated probability of exposure, frequency of exposure, average intensity of exposure (mg/hour), and confidence in these industry/job combinations. For other industry/job combinations not evaluated in the review, probability, frequency, intensity, and confidence levels were assigned using the original job exposure matrix (21). The distribution of pesticide-related occupations among parents of cases and controls is provided in appendix table 1.

Probability, defined as the percentage of workers in a particular job/industry combination involving exposure to insecticides, herbicides, or fungicides, was assigned to one of four arbitrary categories: <10 percent, 10–49 percent, 50–89 percent, and ≥ 90 percent. Exposure frequency was assigned a score of 1 to 4 according to the amount of time spent exposed to pesticides: <2, 2–10, >10–≤ 20, or >20 hours/week. Exposure intensity reflected differences roughly corresponding to pesticide exposure levels of <1, 1–<10, 10–100, and >100 mg/hour, which were then given a weight of 1, 7, 70, or 1,000, respectively, for the calculation of cumulative exposure. Assessment of intensity was restricted to dermal exposure, because approximately 95 percent of total exposure to pesticides comes from deposition on the skin (23). Duration of exposure for a given job was estimated as the difference between the start date and the end date multiplied by the proportion of all hours spent on the job. Finally, an overall confidence score, reflecting the level of confidence in all three exposure metrics, was developed for each job on a scale of 1 (lowest) to 3 (highest) as a means of interpreting the potential for misclassification.

For each subject, the exposure assessments and job history were used to estimate cumulative exposure for each substance, which was calculated as the sum of the product of the intensity level weight and the duration of exposure across jobs. Cumulative exposure was examined during four time windows relative to the index pregnancy and birth: throughout the entire work history before the reference date (i.e., the diagnosis date for cases); within 1 month before the index pregnancy; during the index pregnancy; and after the birth of the index child. Cumulative exposure for the entire work history was classified into three categories (low, medium, high) based on the 50th and 75th percentiles of exposure among exposed controls. Cumulative exposures in the other time windows of exposure were classified into two categories based on the 50th percentile of exposure among exposed controls, because lower exposure rates were reported. The reference group consisted of parents exposed to none of the three groups of pesticides in all jobs. This report is based on the direct interview data obtained from 647 mothers (253 cases and 394 controls) and 492 fathers (215 cases and 277 controls). We did not include paternal data provided by mothers in this analysis. Fifty-four mothers and 16 fathers were excluded from the analysis because demographic information was inadequate or module questionnaires were not administered.

We used the chi-squared test and Fisher's exact test for categorical comparisons of data. An unconditional logistic regression model with adjustment for age, sex, and relevant confounders was used to calculate odds ratios and 95 percent confidence intervals as estimates of the relative risk (24). Potentially confounding factors included parental education, race, family income, and parental age at pregnancy. This limited set of variables was chosen to capture potential confounding effects broadly related to socioeconomic status (SES). Tests for trend were performed by treating levels of categorical variables as units forming a continuous variable in the logistic model (25). Analyses were performed with all subjects together and then separately by sex to explore differences in associations between boys and girls. Analyses were also conducted by stratifying the data by the children's age and by the major histologic types of germ-cell tumors. Paternal exposure was analyzed for direct interview data only. Statistical analyses were performed using the statistical package SAS (version 8.0; SAS Institute, Inc., Cary, North Carolina). All tests were two-tailed.

RESULTS

Demographic characteristics are shown in table 1. Boys ($n = 73$) and girls ($n = 180$) accounted for 28.9 percent and 71.2 percent of total case subjects, respectively ($p < 0.001$). Approximately 50 percent of cases were younger than age 2 years at diagnosis. No differences between cases and controls were found for gestational age at birth, maternal age at index pregnancy, paternal educational attainment, or paternal race. Case families tended to have a lower annual household income than control families. There were more cases than controls in the lowest and highest birth weight groups. Case mothers tended to have lower levels of education and were more likely to be Nonwhite. Case fathers were older at the birth of the index child than were control fathers.

Generally, more case mothers (37.5 percent) than control mothers (27.9 percent) had ever experienced occupational pesticide exposure during their lifetime (table 2). After adjustment for child's age, child's sex, maternal age at index pregnancy, maternal education, maternal race, and family income, the odds ratio associated with maternal occupational exposure was 1.2 (95 percent confidence interval (CI): 0.9, 1.5). Cumulative maternal occupational exposure before the index pregnancy, within 1 month before the index pregnancy, during the index pregnancy, or after the birth of the index child did not alter the odds ratio substantially from the null. Similarly, no change in risk was seen when data were analyzed by estimated occupational exposure level in different time windows. For example, the odds ratios associated with maternal exposures at the medium level or higher before and during the index pregnancy were 1.1 (95 percent CI: 0.7, 1.5) and 0.9 (95 percent CI: 0.5, 1.7), respectively. Because only

TABLE 1. Distribution of data on demographic and potentially confounding factors and odds ratios for germ-cell tumors in a case-control study of germ-cell tumors and parental occupational pesticide exposure, Children's Oncology Group, United States, 1993–2001

Variable	Cases ($n = 253$)		Controls ($n = 394$)		Odds ratio*	95% confidence interval	*p* value
	No.	%	No.	%			
Sex							
Male	73	28.9	169	42.9			<0.001†
Female	180	71.2	225	57.1			
Child's age (years)							
0	50	19.8	86	21.8			0.04†
1–2	68	26.9	71	8.0			
3–10	63	24.9	123	31.2			
11–14	72	28.5	114	28.9			
Gestational age (weeks)							
≤37	44	17.4	55	14.0	1.3	0.8, 2.0	
38–41	187	73.9	304	77.2	1.0		
>41	22	8.7	35	8.9	1.0	0.6, 1.8	
Maternal age (years) at index pregnancy							
≤24	68	26.9	98	24.9	1.1	0.7, 1.6	
25–31	128	50.66	198	50.3	1.0		
≥32	57	22.5	98	24.9	0.9	0.6, 1.3	
Paternal age (years) at birth of index child							
≤26	60	27.9	59	21.3	1.5	1.0, 2.4	<0.05
27–32	82	38.1	124	44.8	1.0		
≥33	73	34.0	94	33.9	1.2	0.8, 1.8	
Maternal education							
High school or less	96	37.9	110	27.9	1.0		
College (4 years) or equivalent	74	29.3	133	33.8	0.6	0.4, 0.9	<0.05
More than college	83	32.8	151	38.3	0.6	0.4, 0.9	<0.05
Annual family income ($US)							
≤20,000	70	28.0	72	18.5	1.0		
20,001–30,000	59	23.6	100	25.6	0.6	0.4, 1.0	<0.05
30,001–50,000	61	24.4	120	30.8	0.5	0.3, 0.8	<0.05
>50,000	60	24.0	98	25.1	0.6	0.4, 1.0	<0.05
Paternal education							
High school or less	78	36.3	90	32.5	1.0		
College (4 years) or equivalent	51	23.7	69	24.9	0.9	0.5, 1.4	
More than college	86	40.0	118	89.4	0.8	0.6, 1.3	
Paternal race							
White	179	83.3	244	88.1	1.0		
Nonwhite	36	16.7	33	11.9	0.5	0.9, 2.5	
Birth weight (g)							
<3,000	67	26.5	93	23.6	1.4	0.9, 2.1	
3,000–3,500	75	29.6	147	37.3	1.0		
3,501–4,000	66	26.1	111	28.2	1.2	0.8, 1.8	
>4,000	45	17.8	43	10.9	2.1	1.2, 3.4	<0.05
Maternal race							
White	198	78.3	337	85.5	1.0		
Nonwhite	55	21.7	57	14.5	1.6	1.1, 2.5	<0.05

* Odds ratio from logistic regression.
† *p* value from chi-squared test.

TABLE 2. Relation between self-reported cumulative maternal occupational exposure to pesticides and risk of malignant germ-cell tumors in children, Children's Oncology Group, United States, 1993–2001

Exposure to pesticides	Total				Boys				Girls			
	No. of cases ($n = 253$)	No. of controls ($n = 394$)	OR*,†	95% CI*	No. of cases ($n = 73$)	No. of controls ($n = 169$)	OR†	95% CI	No. of cases ($n = 180$)	No. of controls ($n = 225$)	OR†	95% CI
Lifetime exposure												
Never exposed	158	284	1.0		50	126	1.0		108	158	1.0	
Ever exposed	95	110	1.2	0.9, 1.5	23	43	1.2	0.7, 2.0	72	67	1.2	0.9, 1.6
Low	52	57	1.2	0.9, 1.7	16	19	1.4	0.8, 2.6	36	38	1.1	0.8, 1.7
Medium or higher	43	53	1.1	0.8, 1.6	7	24	0.8	0.3, 1.8	36	29	1.2	0.8, 1.8
p for trend‡			0.36				0.99				0.30	
Exposure before pregnancy												
Never exposed	182	296	1.0		55	130	1.0		127	166	1.0	
Ever exposed	71	97	1.0	0.8, 1.4	18	39	1.0	0.6, 1.8	53	58	1.0	0.7, 1.4
Low	35	47	1.0	0.7, 1.5	10	13	1.2	0.6, 2.4	25	34	0.9	0.6, 1.4
Medium or higher	36	50	1.1	0.7, 1.5	8	26	0.9	0.4, 1.8	28	24	1.2	0.7, 1.8
p for trend‡			0.80				0.83				0.66	
Exposure 1 month before pregnancy												
Never exposed	230	364	1.0		66	158	1.0		164	206	1.0	
Ever exposed	23	29	1.0	0.7, 1.6	7	11	1.2	0.5, 2.9	16	18	0.9	0.5, 1.6
Exposure during pregnancy												
Never exposed	224	361	1.0		65	157	1.0		159	204	1.0	
Ever exposed	29	32	1.1	0.7, 1.6	8	12	1.3	0.6, 2.8	21	20	1.0	0.6, 1.7
Low	16	15	1.2	0.7, 2.1	6	5	1.7	0.7, 4.2	10	10	1.1	0.5, 2.1
Medium or higher	13	17	0.9	0.5, 1.7	2	7	0.7	0.2, 3.1	11	10	1.0	0.5, 1.9
p for trend‡			0.93				0.88				1.00	
Exposure after giving birth												
Never exposed	216	357	1.0		66	154	1.0		150	203	1.0	
Ever exposed	37	35	1.3	0.9, 1.8	7	14	1.4	0.6, 3.3	30	21	1.3	0.8, 1.9
Low	24	17	1.5	0.9, 2.3	6	8	1.6	0.7, 4.0	18	9	1.4	0.9, 2.4
Medium or higher	13	18	1.0	0.6, 1.8	1	6	0.7	0.1, 5.5	12	12	1.1	0.6, 2.0
p for trend‡			0.50				0.72				0.49	

* OR, odds ratio; CI, confidence interval.

† All odds ratios were adjusted for child's sex, child's age, maternal education, maternal race, maternal age at index pregnancy, and family income.

‡ Trend test for the comparison between no exposure (never exposed), low exposure, and medium exposure or higher.

a few mothers had been exposed to pesticides 1 month before the index pregnancy, we did not analyze data by the amount of exposure during that period. A similar pattern was observed for girls and boys. We also analyzed data for maternal exposure to herbicides, insecticides, and fungicides separately during each of the five time windows. An association between maternal exposure to herbicides after birth and risk of germ-cell tumors in girls was observed (odds ratio = 2.3, 95 percent CI: 1.0, 5.2; data not shown).

Table 3 shows the association between paternal pesticide exposure and childhood germ-cell tumor risk. Fewer case fathers (30.7 percent) than control fathers (36.5 percent) reported occupational exposure. Most risk estimates were less than unity for paternal pesticide exposure in the different time windows. For fathers who had ever been exposed to pesticides, the odds ratios were 0.9 (95 percent CI: 0.7, 1.2) before pregnancy, 0.8 (95 percent CI: 0.5, 1.3) within 1 month before pregnancy, 0.8 (95 percent CI: 0.5, 1.2) during pregnancy, and 0.8 (95 percent CI: 0.5, 1.3) after the birth of the index child. When both parents had ever been occupationally exposed to pesticides before the index pregnancy, the odds ratio was 0.8 (95 percent CI: 0.4, 1.3).

We also evaluated the effect of paternal occupational pesticide exposure for those with a probability greater than 1, confidence greater than 1, or both (data not shown). Again, fewer case fathers than control fathers had incurred exposure to pesticides. Among fathers who had ever been exposed to pesticides, the odds ratio was 0.7 (95 percent CI: 0.5, 1.1) for a probability greater than 1, 0.8 (95 percent CI: 0.6, 1.1) for confidence greater than 1, and 0.7 (95 percent CI: 0.5, 1.1) for both probability and confidence greater than 1. Because few mothers had occupational exposure with a probability greater than 1, confidence greater than 1, or both, we did not assess data for these categories.

We conducted further analyses after stratifying the data by age at diagnosis ($\leq$2 years vs. >2 years) and histologic type (mainly dysgerminoma, yolk-sac tumor, and immature teratoma) (table 4). Age at diagnosis did not appear to modify

TABLE 3. Relation between self-reported cumulative paternal and parental occupational exposure to pesticides and risk of malignant germ-cell tumors in children, Children's Oncology Group, United States, 1993–2001

Exposure to pesticides	Total				Boys				Girls			
	No. of cases ($n = 215$)	No. of controls ($n = 277$)	OR*,†	95% CI*	No. of cases ($n = 65$)	No. of controls ($n = 113$)	OR†	95% CI	No. of cases ($n = 150$)	No. of controls ($n = 164$)	OR†	95% CI
Lifetime exposure												
Never exposed	149	176	1.0		52	74	1.0		97	102	1.0	
Ever exposed	66	101	0.8	0.6, 1.1	13	39	0.6	0.3, 1.1	53	62	1.0	0.7, 1.4
Low	34	50	0.9	0.6, 1.3	9	20	0.7	0.3, 1.5	25	30	1.0	0.6, 1.6
Medium	21	25	0.9	0.5, 1.4	2	8	0.5	0.1, 2.1	19	17	1.0	0.6, 1.7
High	11	26	0.6	0.3, 1.2	2	11	0.3	0.1, 1.4	9	15	0.8	0.4, 1.6
p for trend‡			0.16				0.06				0.70	
Exposure before pregnancy												
Never exposed	151	185	1.0		52	78	1.0		99	107	1.0	
Ever exposed	61	92	0.9	0.7, 1.2	13	35	0.7	0.3, 1.2	48	57	1.0	0.7, 1.4
Low	29	44	0.9	0.6, 1.3	8	17	0.7	0.3, 1.6	21	27	1.0	0.6, 1.6
Medium or higher	32	48	0.9	0.6, 1.3	5	18	0.5	0.2, 1.4	27	30	1.0	0.6, 1.6
p for trend§			0.49				0.16				0.97	
Exposure within 1 month before pregnancy												
Never exposed	190	242	1.0		64	103	1.0		126	139	1.0	
Ever exposed	22	35¶	0.8	0.5, 1.3	1	10	0.2	0.0, 1.5	21	25¶	1.0	0.6, 1.6
Low	8	16	0.7	0.4, 1.5	1	4	0.4	0.1, 3.2	7	12	0.8	0.4, 1.9
Medium or higher	14	18	0.9	0.5, 1.6	0	6	0		14	12	1.1	0.6, 1.9
p for trend§			0.56				0.12				0.93	
Exposure during pregnancy												
Never exposed	189	237	1.0		63	101	1.0		126	136	1.0	
Ever exposed	23	40	0.8	0.5, 1.2	2	12	0.3	0.1, 1.3	21	28	0.9	0.5, 1.5
Low	8	18	0.7	0.3, 1.4	1	5	0.4	0.0, 2.6	7	13	0.8	0.4, 1.7
Medium or higher	15	22	0.8	0.5, 1.4	1	7	0.3	0.0, 2.1	14	15	0.9	0.5, 1.7
p for trend§			0.31				0.13				0.74	
Exposure after birth of index child												
Never exposed	187	240	1.0		64	102	1.0		123	138	1.0	
Ever exposed	25	37	0.8	0.5, 1.3	1	11	0.2	0.0, 1.4	24	26	1.0	0.6, 1.6
Low	12	18	0.8	0.5, 1.5	0	6	0.0		12	12	1.0	0.6, 1.9
Medium or higher	13	19	0.8	0.5, 1.5	1	5	0.4	0.0, 2.7	12	14	0.9	0.5, 1.8
p for trend§			0.43				0.15				0.89	
Parental occupational exposure to pesticides before pregnancy#												
Neither parent exposed	107	132	1.0		41	54	1.0		66	78	1.0	
Mother exposed	32	34	1.1	0.7, 1.6	11	17	0.9	0.4, 1.8	21	17	1.1	0.7, 1.9
Father exposed	39	61	0.9	0.6, 1.3	8	26	0.5	0.2, 1.1	31	35	1.1	0.7, 1.8
Both parents exposed	16	27	0.8	0.4, 1.3	2	8	0.4	0.1, 1.8	14	19	0.8	0.5, 1.5

* OR, odds ratio; CI, confidence interval.

† Unless otherwise specified, odds ratios were adjusted for child's sex, child's age, paternal education, paternal race, paternal age at index pregnancy, and family income.

‡ Trend test for the comparison between no exposure (never exposed), low exposure, medium exposure, and high exposure.

§ Trend test for the comparison between no exposure (never exposed), low exposure, and medium exposure or higher.

¶ Quantitative data on exposure were missing for one subject.

Odds ratios were adjusted for child's sex, child's age, parental education, parental race, parental age at index pregnancy, and family income.

TABLE 4. Relation between self-reported cumulative parental occupational exposure to pesticides and risk of malignant germ-cell tumors in children, by histologic type and age, Children's Oncology Group, United States, 1993–2001

Exposure to pesticides*	No. of cases	No. of controls	Odds ratio	95% confidence interval
	Mothers†			
Dysgerminoma				
Never exposed	18	284	1.0	
Ever exposed	16	110	1.9	0.9, 4.2
Yolk-sac tumor				
Never exposed	64	284	1.0	
Ever exposed	39	110	1.2	0.8, 1.8
Immature teratoma				
Never exposed	34	284	1.0	
Ever exposed	19	110	1.1	0.6, 2.1
Child's age at diagnosis				
≤2 years				
Never exposed	73	110	1.0	
Ever exposed	45	47	1.1	0.7, 1.7
>2 years				
Never exposed	85	174	1.0	
Ever exposed	50	63	1.2	0.8, 1.8
	Fathers‡			
Dysgerminoma				
Never exposed	17	176	1.0	
Ever exposed	7	101	1.0	0.4, 2.5
Yolk-sac tumor				
Never exposed	62	176	1.0	
Ever exposed	31	101	0.9	0.5, 1.4
Immature teratoma				
Never exposed	29	176	1.0	
Ever exposed	15	101	1.1	0.6, 2.1
Child's age at diagnosis				
≤2 years				
Never exposed	74	77	1.0	
Ever exposed	37	46	0.9	0.6, 1.4
>2 years				
Never exposed	75	99	1.0	
Ever exposed	29	55	0.8	0.5, 1.2

* Exposure information was derived by combination of the metrics implemented for different time windows.

† Odds ratios were adjusted for child's sex, child's age, maternal education, maternal race, age at index pregnancy, and family income.

‡ Odds ratios were adjusted for child's sex, child's age, paternal education, maternal race, age at index pregnancy, and family income. Data came from the father's self-report of pesticide exposure.

the association with parental exposure. Maternal exposure was associated with an approximately twofold, though statistically nonsignificant, increased risk of dysgerminoma (odds ratio = 1.9, 95 percent CI: 0.9, 4.2). The odds ratios for other types of germ-cell tumors associated with parental occupational exposure to pesticides were all close to unity.

The numbers of occupational modules used in the study and occupational exposure by all measurements shown in tables 2–4 were analyzed according to parental educational attainment and family income. (Paternal information is shown in appendix table 2.) We found that the number of modules applied appeared to be slightly inversely associated with SES. However, the pattern was consistent across cases and controls. Similarly, there was also some evidence suggesting that occupational exposure was less common among children whose parents had more education or a higher family income as compared with their counterparts. Again this pattern did not appear to vary by case-control status.

DISCUSSION

Several pesticides have been shown to be carcinogenic in in-vitro studies (26). Epidemiologic studies have linked pesticide exposure to increased risk of several childhood cancers (27, 28), with the evidence being most consistent for leukemia (29), central nervous system tumors (27, 30), and neuroblastoma (31). However, evidence has been less consistent for all childhood cancers combined, kidney cancer, and the other types of childhood cancer (22, 32–34). Most previous studies of pesticides and childhood cancer have lacked detailed information on frequency and type of pesticide exposure or have estimated exposure on the basis of job title or industry (27, 28, 35). The latter method is generally considered a poor proxy for identifying and quantifying specific exposures (12) and is probably strongly associated with SES and lifestyle factors.

To our knowledge, only five studies conducted since 1982 have focused on determining risk factors for germ-cell tumors in children. Two of them were carried out in the United States (9, 36) and included 73 and 105 germ-cell tumor cases, respectively. Two British studies (8, 37) included 41 and 87 cases, respectively, and one Mexican study (38) included 21 cases. Only two of these studies investigated parental occupational exposure to pesticides and other chemicals, and those assessments mostly defined exposure simply as whether a parent had ever held a job involving pesticide exposure (8, 9).

In the current study, we administered both a generic questionnaire and job-specific questionnaires to collect information on job titles and specific information on each job. We evaluated this information for pesticide exposure using a pesticide job exposure matrix while taking into consideration hours of work, duties, protection used, products produced, and duration of employment. Our method of exposure assessment attempted to take into account exposure variability within jobs due to specific tasks, processes, and technology. The intensity and duration of exposure were also estimated, thus allowing a more comprehensive evaluation of occupational exposure to pesticides. In general, we found that parental occupational exposure to pesticides was not related to increased risk of germ-cell tumors in offspring.

Previous studies of germ-cell tumors in adults have suggested that such tumors might be caused by exposures incurred early in life or in utero, most probably before birth (11, 39, 40). This study focused on relations between parental

pesticide exposure in four time windows (before pregnancy, within 1 month before pregnancy, during pregnancy, and after the birth of the index child) and childhood germ-cell tumor risk. In this study, which to our knowledge is the largest and most comprehensive case-control study of childhood germ-cell tumors to date, we found no strong evidence of an overall association between parental occupational exposure to pesticides and risk of germ-cell tumors among offspring. This is similar to a previous study (9) that found no association with parental pesticide exposure. Another descriptive epidemiologic study found increased risk of testicular cancer in the offspring of male pesticide applicators (10). The few positive findings from our study, including a positive association between maternal herbicide exposure during the postnatal period and germ-cell tumors among girls and a nonsignificant positive association between maternal pesticide exposure and dysgerminoma, were based on small samples and need to be confirmed in future studies.

It is interesting that paternal pesticide exposure was inversely associated with germ-cell tumor risk, although the point estimates were mostly nonsignificant. The small number of exposed subjects and the multiple comparisons involved in the analyses suggest a cautious interpretation. Nevertheless, this pattern was also reported in an earlier investigation: A Danish study found that offspring of fathers employed in agriculture had a marginally reduced risk of germ-cell tumors, although the offspring were older than 16 years (11). Pesticide exposure in males has been associated previously with a reduced sperm-cell count (41, 42) and an increased number of female offspring (43, 44). More studies are needed to investigate the possible gender-specific effects of paternal pesticide exposure on offspring.

Our study had several strengths. First, these findings represent the most recent information available on childhood germ-cell tumors in the United States. Second, detailed exposure information was available for many pesticide-exposed jobs and covered the likely relevant periods of exposure. Third, the exposure information was collected from both mothers and fathers. Fourth, the relatively large sample size allowed us, in the analyses, to stratify the data by gender, age at diagnosis, histologic type, kind of pesticide, and exposure probability and confidence. Fifth, we were able to assess each parental subject's pesticide exposure according to specifics of employment during his/her life, such as industry, job title, hours of work, duties, protection used, products produced, and duration of employment. Thus, the exposure assessment more closely reflected the actual occupational pesticide exposure of our cases and controls. Last, although residential exposure to pesticides was not included in this report, additional adjustment for residential pesticide exposure did not alter the parental occupational exposure associations reported. Detailed results on the association of residential exposure to pesticides and other chemicals with germ-cell tumor risk will be presented in a separate paper (45).

The results of this study must be interpreted by recognizing several limitations. First, the relatively low response rate, particularly among controls (80.8 percent for cases and 66.6 percent for controls), raises a concern about selection bias. Using random digit dialing to identify control households may have excluded families of lower SES (46). In our study, there were fewer controls from lower-SES families than cases. For both cases and controls, we found that the number of module questionnaires implemented and the number of pesticide exposures were inversely related to SES. If participation in the study differed according to SES and case-control status (i.e., if potential control parents with low SES were more likely to refuse participation than case parents with the same SES), the association between parental occupational exposure and childhood germ-cell tumors might have been underestimated. Second, the job information reported by parents could have been subject to misclassification. However, the occupational module questionnaires used in the study were designed to collect detailed information on jobs that each parental subject had held during his/her life—including information on industry, job title, working hours, duties, materials used, products produced, and duration of employment—rather than focus only on specific chemical exposures. The module questionnaire data were then reviewed and exposure levels were assigned with case-control status masked. Although we could not completely exclude the possibility of differential recall by case parents and control parents, the procedure applied in the study should have minimized differential misclassification in the exposure assessment. Third, although considerable effort was made to ensure the quality of the exposure assessment, nondifferential misclassification of exposure undoubtedly occurred and would have biased the risk associations toward the null. Fourth, because of the low rate of exposure to pesticides and the relatively small sample size, this study had more than 80 percent statistical power to detect an odds ratio of 1.5 or higher for ever exposure to pesticides or exposure during the preconception period and an odds ratio of 2.0 or higher for in-utero or postnatal exposure. Last, germ-cell tumors comprise a number of different histologic subtypes; each type derives from distinct cells and may have a distinct etiology, which restricts the ability of any single study to detect significant case-control differences.

In summary, this study failed to find strong evidence in support of a relation between parental exposure to pesticides in the workplace and an increased risk of germ-cell tumors in offspring.

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APPENDIX TABLE 1. Distribution of pesticide-related occupations/industries among parents of cases and controls in a case-control study of germ-cell tumors and parental occupational pesticide exposure, Children's Oncology Group, United States, 1993–2001

Standard Occupational Classification code*	Job title(s)†	Cases			Controls		
		Total no.	Exposed to pesticides		Total no.	Exposed to pesticides	
			No.	%		No.	%
12 and 13	Officials and administrators, others	203	33	16	225	35	16
20, 23, 46, and 47	Other white-collar jobs	105	3	3	136	4	3
42 and 43	Sales occupations	51	5	10	75	10	13
52	Service occupations, except private household and protective	66	40	61	66	47	71
55	Farm operators and managers	8	7	88	22	17	77
56	Other agricultural and related occupations	30	24	80	32	24	75
61	Mechanics and repairers	91			115	6	5
64	Construction trades	57	15	26	75	23	31
68	Precision production occupations	15	10	67	15	6	40
75 and 76	Machine operators and tenders	56	3	5	76	5	7
82	Transportation occupations	74	2	1	59	3	2
86	Helpers	8	2	25	16	3	19
87	Handlers, equipment cleaners, and laborers	60	12	20	49	11	22

* Jobs were assigned two-digit Standard Occupational Classification codes (19) based on the job title and the type of industry.

† Subjects could appear in multiple categories if their parents had held jobs in more than one category. Job categories with fewer than five subjects whose parents were exposed to pesticides were not included in the table. These categories were: management-related occupations; veterinarians; social, recreation, and religious workers; teachers, except those at postsecondary institutions; athletes and related workers; forestry and logging workers; production supervisors, including precision production; plant and system operators; fabricators, assemblers, and hand workers; material movers, except transportation workers; and military personnel.

APPENDIX TABLE 2. Prevalence (%) of paternal occupational pesticide exposure by annual family income in a case-control study of germ-cell tumors and parental pesticide exposure, Children's Oncology Group, United States, 1993–2001

Exposure to pesticides	Cases				Controls			
	≤$20,000	$20,001–$30,000	$30,001–$50,000	>$50,000	≤$20,000	$20,001–$30,000	$30,001–$50,000	>$50,000
Lifetime exposure								
Never exposed	68.9	67.9	63.3	78.1	59.3	50.5	64.8	80.2
Ever exposed								
Low	6.6	13.2	23.3	17.2	20.3	21.5	19.4	11.5
Medium	11.5	11.3	6.7	3.1	10.2	14.0	8.3	3.1
High	13.1	7.6	6.7	1.6	10.2	14.0	7.4	5.2
p value		0.06				0.01		
Exposure before pregnancy								
Never exposed	74.5	68.6	63.3	77.8	60.0	55.2	67.0	81.9
Ever exposed								
Low	3.9	9.8	21.7	15.9	26.0	17.2	16.5	9.6
Medium or higher	21.6	21.6	15.0	6.4	14.0	27.6	16.5	8.5
p value		0.02				<0.01		
Exposure 1 month before pregnancy								
Never exposed	92.7	76.1	86.4	96.1	75.0	71.6	84.2	96.3
Ever exposed								
Low	0.0	6.5	6.8	2.0	10.0	11.9	11.0	1.3
Medium or higher	7.3	17.4	6.8	2.0	15.0	16.4	4.9	2.5
p value		0.04				<0.01		
Exposure during pregnancy								
Never exposed	92.7	76.1	84.4	96.1	71.4	68.6	82.1	96.3
Ever exposed								
Low	0.0	8.7	6.7	2.0	9.5	14.3	11.9	1.3
Medium or higher	7.3	15.2	8.9	2.0	19.1	17.1	6.0	2.5
p value		0.07				<0.01		
Exposure after birth of index child								
Never exposed	79.2	79.6	86.4	96.1	71.4	70.6	84.2	97.5
Ever exposed								
Low	8.3	9.1	6.8	3.9	14.3	13.2	8.5	1.3
Medium or higher	12.5	11.4	6.8	0.0	14.3	16.2	7.3	1.3
p value		0.11				<0.01		